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CLINICAL/ORIGINAL PAPERS

Association between coronary flow reserve, left ventricular systolic function, and myocardial viability in acute myocardial infarction

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Aims To investigate the relationships between coronary flow reserve (CFR), left ventricular (LV) systolic function, and myocardial viability in patients with acute myocardial infarction (AMI).

Methods and results In 149 patients with a first AMI, we estimated CFR non-invasively and assessed LV systolic function with low-dose dobutamine Doppler echocardiography (LDDE), which also identified viability. Resting echocardiographic variables did not differ between patients with preserved (54.4%) and low CFR (45.6%). During LDDE, longitudinal LV function was decreased [9.5 cm/s (8;11.3) vs. 10.6 cm/s (8.5;12.5), $P = 0.04$] and end-systolic volume increased [49.5 mL (38;66) vs. 42 (31;61), $P = 0.04$] in patients with low compared with preserved CFR. Among 87 (58%) patients with resting wall motion abnormalities, 28 met the criteria for viability. One of 53 (2%) met the criteria for viability in patients with CFR ≤ 2 compared with 27 of 34 (79%) with CFR > 2, $P < 0.0001$.

Conclusion Resting echocardiographic parameters were similar in patient groups. During LDDE, patients with reduced CFR had increased LV size and compromised longitudinal function of LV and were less likely to have evidence of myocardial viability.

Keywords Coronary flow reserve • Transthoracic echocardiography • Acute myocardial infarction • Viability • Dobutamine stress test • Microcirculation • Left ventricle

Introduction

Despite early reperfusion clinical outcome and recovery of myocardial contractility after successful reperfusion are influenced by the extent of microvascular damage and the persistence of viable myocardium.[1–3] As the optimal reperfusion therapy should restore not only epicardial patency and flow but also myocardial tissue perfusion, the evaluation of coronary flow reserve (CFR) in patients with acute myocardial infarction (AMI) may be important. Diminished CFR provides information about the ability of compensating mechanisms in the vasomotor function of the myocardium. A non-invasive estimate of CFR may be obtained using transthoracic echocardiography that correlate well with CFR measured by other methods.[4,5]

Although CFR and stress testing have been used to evaluate left ventricular (LV) systolic recovery after AMI,[6,7] little is known of the relation between microvascular dysfunction and LV contractile reserve and presence of viability in consecutive patients presenting with ST-elevation (STEMI) or non-ST-elevation AMI (NSTEMI). Therefore, our objective was to determine the association between CFR and LV function in consecutive patients with AMI.

Methods

Study population

Between January 2006 and August 2008, 190 patients with first AMI admitted to the coronary care unit at Funen Hospital, Svendborg, Denmark were consecutively screened. Inclusion criteria were: (i) documented AMI (dynamic rise in T*n*-T >0.1 μg/L, as well as either typical symptoms, characteristic electrocardiographic changes, or both); (ii) left anterior descending artery (LAD) without any stenosis exceeding 50% by coronary angiography; (iii) an echocardiographic

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window allowing assessment of CFR; (iv) no prior history of documented AMI, coronary bypass surgery, valvular heart disease, and poorly controlled obstructive airways disease; and (vi) no ventricular arrhythmias. Four patients were excluded because of inability to detect coronary flow. Three were excluded because of significant stenosis in LAD. Thirty-four patients did not have low-dose dobutamine echocardiography (LDDE), 27 because of ventricular ectopy or non-sustained ventricular tachycardia, four patients refused testing and three patients had inadequate echocardiographic image quality. Thus, the final study population consisted of 149 patients.

Patients presenting with STEMI within 12 h of onset of symptoms were transferred to a tertiary centre where emergency percutaneous coronary intervention (PCI) was performed. Fibrinolysis was not used in any patients. In patients presenting with NSTEMI, initial antithrombotic treatment was instituted and subsequent angiography performed within 4 days (IQR 3;6).

The study protocol was approved by the Regional Ethics Committee of Southern Denmark, and the Danish Data Protection Agency, and written informed content was obtained from all participating patients.

Two-dimensional and dobutamine Doppler echocardiography

Transthoracic echocardiography was performed median 5 days[3,8] after enrolment using a commercially available ultrasound system (Vivid 7, GE Medical Systems, Inc., Horten, Norway). All images were analysed offline by a single investigator, blinded to all clinical data. After assessment of CFR, patients rested for at least 5 min to ensure that the effect of adenosine had ceased and subsequently, LDDE was performed.

Assessment of coronary flow reserve

The CFR studies were performed in an angiographically non-obstructed LAD (<50%). If a significant stenosis was revealed during angiography, CFR was assessed after the vessel was revascularized.

CFR was assessed in the distal part of LAD. After baseline recordings of flow velocity, adenosine was administered by intravenous infusion (140 μg/kg/min) for 90 s. During infusion, hyperaemic flow profiles were recorded.[8,9] The CFR was estimated to be the ratio of hyperaemic to baseline peak diastolic coronary flow velocities (*Figure 1*). A. CFR > 2 was considered normal and the population dichotomized according to this.[8] All of the subjects abstained from caffeine-containing drinks for at least 12 h before testing.

The intra- and interobserver variability of CFR was assessed in 20 consecutive patients, who underwent dual assessment of coronary flow by two experienced co-investigators. These recordings were analysed by two experienced observers.

Resting echocardiography

From two-dimensional images, regional myocardial function was assessed using regional wall motion according to current guidelines.[10] A wall motion score index (WMSI) was calculated by dividing the sum of scores by the number of visualized segments. LV end-diastolic and end-systolic volumes were measured using biplane planimetry in long-axis views and LV ejection fraction (LVEF) calculated. Longitudinal LV systolic function was assessed using peak systolic velocity measured with pulsed wave tissue Doppler echocardiography. From apical four- and two-chamber views, the velocities were recorded at four sites corresponding to the septal, anterior, lateral, and posterior mitral annulus and the mean value from these four sites was calculated. Stroke volume (SV) and cardiac output (CO) were calculated using the LV outflow tract (LVOT) area and time velocity integral from pulse-wave Doppler recording of LVOT flow. SV was calculated as $\pi \times (LVOT_{diameter}/2)^2 \times$ stroke length. CO was calculated as SV × heart rate.

Low-dose dobutamine echocardiography

After resting images were obtained, LDDE was performed. Dobutamine was infused at dosages of 5 and 10 μg/kg/min for 3 min of each dose. All images were repeated after 3 min infusion of 10 μg/kg/min dobutamine. Pharmacological therapy including beta-blocking agents was not withheld for ethical reasons. Contractile reserve was calculated as $LVEF_{LDDE} - LVEF_{rest}$. Viability was assessed in patients with resting wall motion abnormalities and defined as improved contraction in more than two contiguous segments and a decrease of >0.22 in WMSI. Improved segmental wall motion during LDDE was defined as previously suggested.[11]

Statistical analysis

Analyses were conducted with STATA/MP 10.0 (StataCorp LP, TX, USA). Data are presented as median (inter-quartile range) and compared using Kruskal–Wallis equality-of-populations rank tests for continuous variables, whereas categorical variables are presented as counts (percentage) and compared using χ^2 tests. As significance tests for baseline characteristics are presented for descriptive purposes only, no adjustment for multiple testing was done.

Univariable logistic regression analysis was used to evaluate relation between various clinical, echocardiographic and angiographic variables, and viability. Variables identified in univariable analysis as predictors of viability were subsequently tested in a multivariable model. A $P < 0.05$ was considered statistically significant.

Results

Clinical characteristics of the study population

Clinical characteristics are shown in *Table 1*. Patients with CFR ≤ 2 were older and more frequently males and presented with higher heart rate at admission. In contrast, no difference was found in Killip classification ($P = 0.83$), in the type of infarction (STEMI vs. NSTEMI), culprit vessel or enzymatic size of AMI ($P = 0.64$, $P = 0.87$, and $P = 0.39$, respectively).

Resting left ventricular function

There was no significant difference in resting WMSI, LV end-diastolic, LV end-systolic volumes, or systolic mitral annular velocity (s′) in patients with normal compared with abnormal CFR. We found a slight, but significant, difference in Doppler estimated CO (*Table 2*).

Left ventricular function and haemodynamic response during dobutamine stimulation

During LDDE, LV end-systolic volume, and WMSI were reduced and s′ increased in patients with a normal CFR (CFR > 2) (*Table 2*). In contrast, the change of LVEF, LV end-diastolic volume, CO and SV during LDDE were similar for both groups.

In patients with impaired CFR, LVEF improved 8% (0;14%) and SV increased 13.9 mL (7.6;24.5), $P = 0.0002$ and $P < 0.00001$ compared with rest, respectively, during LDDE. In patients with

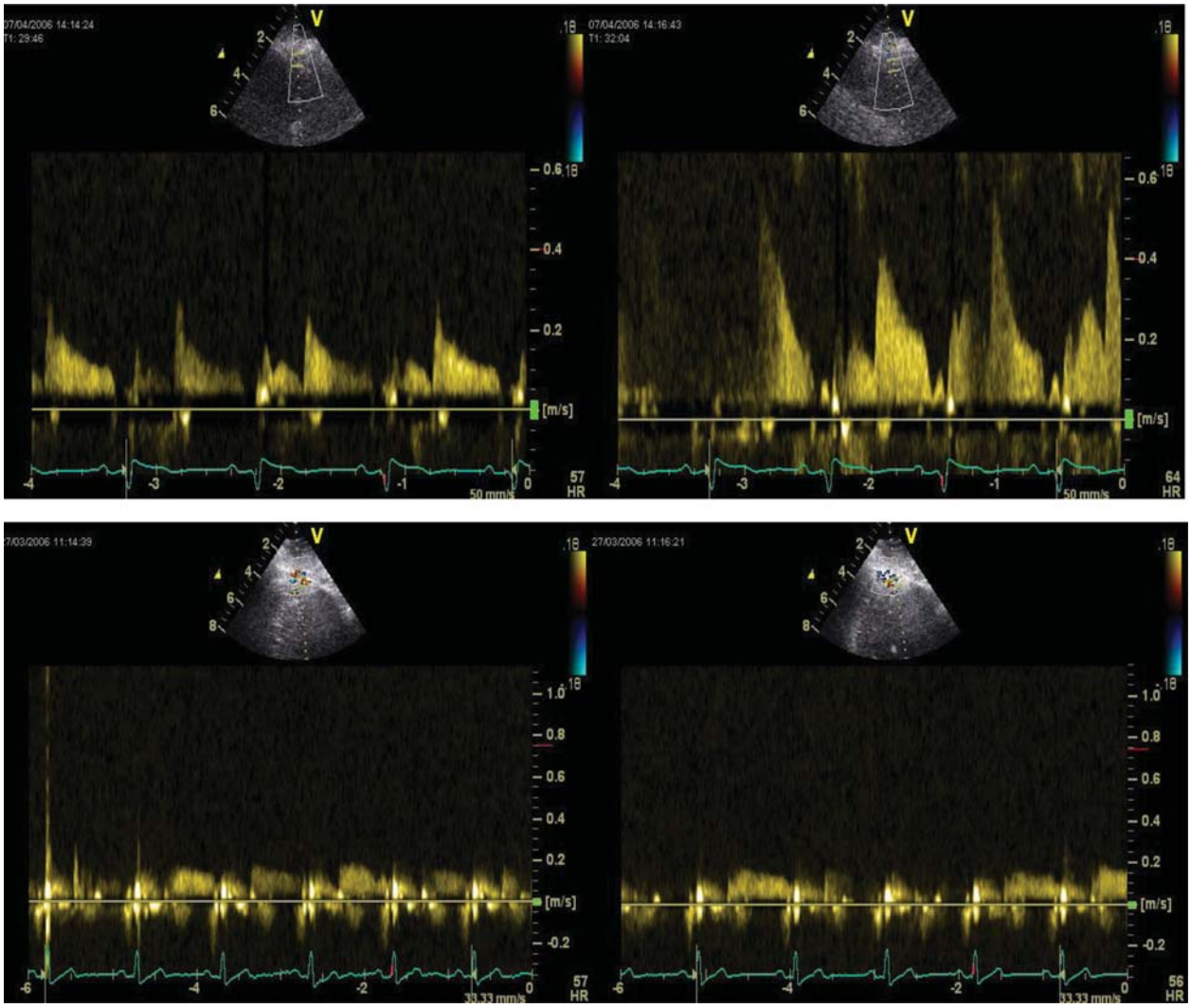

Figure 1 Coronary flow reserve response in two patients with STEMI and culprit in LAD. Normal CFR = 2.2 (top) and diminished CFR = 1.1 (bottom).

preserved CFR, the change in LVEF was 8% (0;15%) and 13.8 mL (3.8;21.9) in SV, $P = 0.0001$ and $P = 0.00001$, respectively.

Myocardial viability

Among 87 patients (58%) with resting wall motion abnormalities, 28 (32%) met the criteria for viability. One of 53 (2%) with CFR ≤ 2 met the criteria for viability compared with 27 of 34 patients (79%) with CFR > 2, $P < 0.0001$. Additionally, after adjustment for age, gender, resting heart rate, resting LVEF, resting blood pressure, STEMI vs. NSTEMI, culprit vessel, and enzymatic size of AMI, the absence of viability in the 87 patients with resting wall motion abnormalities was highly significantly associated with decreased microcirculation, $P < 0.0001$.

In patients with resting wall motion abnormalities, baseline LV systolic function assessed with LVEF was 44% (36;51) in patients with CFR ≤ 2 and 44% (35;51) in patients with normal CFR, $P = 0.95$. Furthermore, SV and s' were also similar in both groups. SV and s' in CFR ≤ 2 were 64.1 mL (52.9;77.3) and 6.7 cm/s (6;8.1) and in the group with normal CFR SV was 62.3 mL (52.6;71.5) and s' was 6.7 cm/s (6.0;8.1), $P = 0.57$ and $P = 0.95$, respectively.

Among patients with resting wall motion abnormalities, change in LVEF was 8% (0;16) in patients with CFR ≤ 2 and 12% (5;17) in patients with CFR > 2, $P = 0.1$, and change in SV was 14.2 ml [4;21.7] in patients with CRF ≤ 2 and 11.5 l/min [6.2;25.4] in patients with CFR > 2 $P = 0.84$. Furthermore, changes in s' were 2.0 cm/s [1.3;3.1] in patients with CFR ≤ 2 and 2.5 cm/s [1.6;3.55] in patients with CFR > 2 in this subgroup, $P = 0.1$.

The intra- and interobserver variability of coronary flow reserve

The interobserver variability were baseline coronary flow: mean difference: 0.003; 95% limits of agreement (LOA): −0.03 to 0.04; CV: 5.3% and CFR: mean difference: 0.004; 95% LOA: −0.04 to

Table 1 Clinical characteristics

	CFR ≤ 2	CFR > 2	*P*-value
Patients, *n*	86	63	
Age (years)	64 (58;74)	58 (51;68)	0.009
Gender (female/male)	24/62	16/47	0.12
Height (cm)	174.5 (167;180)	174 (168;179)	0.84
Weight (kg)	80.4 (69.7;90)	80 (71;90.6)	0.82
BMI (kg/m^2)	26.6 (23.1;29.6)	27.1 (23.8;30.1)	0.43
Systolic BP (mmHg)	140 (122;160)	138 (121;157)	0.8
Diastolic BP (mmHg)	80 (70;95)	80 (75;90)	0.6
Heart rate (b.p.m.)	65 (58;73)	60 (54;68)	0.044
Total cholesterol (mmol/L)	4.2 (3.8;5)	4.7 (3.9;5.4)	0.02
LDL (mmol/L)	2.4 (2.1;3)	2.8 (2.1;3.3)	0.12
HDL (mmol/L)	1.1 (0.86;1.37)	1.2 (0.92;1.37)	0.4
Triglyceride (mmol/L)	1.33 (0.89;1.67)	1.22 (0.9;1.6)	0.9
Troponine-T (μg/L)	1 (0.39;4.47)	1.05 (0.29;2.53)	0.3
Current smoker, *n*	46	37	0.4
fBG (mmol/L)	5.6 (5.3;6.3)	5.6 (5.2;6.1)	0.25
STEMI/NSTEMI, *n*	37/49	31/32	0.22

CFR, coronary flow reserve; BMI, body mass index; BP, blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; fBG, fasting blood glucose; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction.

Table 2 Echocardiographic findings at baseline and low-dose dobutamine Doppler echocardiography

	CFR ≤ 2	CFR > 2	*P*-value
Baseline			
LVEDV (mL)	118 (97;141)	108 (93;124)	0.13
LVESV (mL)	57.5 (46;78)	51 (40;66)	0.11
WMSI	1.19 (1;1.63)	1.13 (1;1.44)	0.2
LVEF (%)	52 (42;57)	54 (44;60)	0.2
s′ (cm/s)	7.0 (6.3;8.6)	7.2 (6.3;8.5)	0.7
Stroke volume (mL)	67 (57;77)	64 (54;74)	0.27
Cardiac output (L/min)	4.4 (3.7;5.2)	3.8 (3.2;4.8)	0.02
Dobutamine stimulation			
LVEDV (mL)	121.5 (100;153)	114 (99;134)	0.1
LVESV (mL)	49.5 (38;66)	42 (31;61)	0.04
WMSI	1.09 (1.00;1.56)	1.00 (1.00;1.13)	0.01
LVEF (%)	61 (55;68)	60 (49;66)	0.9
s′ (cm/s)	9.5 (8.0;11.3)	10.6 (8.5;12.5)	0.04
Stroke volume (mL)	83 (67;97)	80 (62;97)	0.72
Cardiac output (L/min)	5.8 (4.7;6.6)	5.2 (4.2;6.9)	0.6
Reserves			
LVEDV (mL)	2.5 (−11;21)	3 (−7;19)	0.98
LVESV (mL)	−5 (−19;4)	−8 (−17;1)	0.76
WMSI	0 (0;0.0625)	0.005 (0;0.3)	<0.00001
LVEF (%)	8 (0;14)	8 (0;15)	0.44
s′ (cm/s)	2.25 (1.3;3.25)	2.9 (1.8;4.3)	0.002
Stroke volume (mL)	13.8 (3.8;21.9)	13.9 (7.6;24.5)	0.5
Cardiac output (L/min)	1.1 (0.4;2.1)	1.6 (0.6;2.2)	0.16

LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; WMSI, wall motion score index; LVEF, left ventricular ejection fraction; *s′*, systolic mitral annular velocity.

Table 3 Angiographic data

	CFR ≤ 2 (*n* = 86)	CFR > 2 (*n* = 63)	*P*-value
No significant vessel disease, *n* (%)	6 (7)	8 (13)	0.18
One-vessel disease, *n* (%)	49 (57)	40 (63)	0.42
Two-vessel disease, *n* (%)	23 (27)	11 (18)	0.18
Three-vessel disease, *n* (%)	8 (9)	4 (6)	0.51
Culprit lesion			
Left anterior descending, *n* (%)	39 (45)	27 (42)	0.87
Right coronary artery, *n* (%)	31 (36)	18 (29)	0.34
Left circumflex, *n* (%)	16 (19)	18 (29)	0.1
Coronary angiography before intervention			
TIMI flow grade			
0, *n* (%)	35 (41)	26 (41)	0.62
1/2, *n* (%)	18 (21)	9 (14)	0.43
3, *n* (%)	33 (38)	28 (44)	0.46
Coronary angiography after intervention			
TIMI flow grade			
0, *n* (%)	3 (3)	0 (0)	0.13
1/2, *n* (%)	9 (11)	6 (10)	0.53
3, *n* (%)	74 (86)	57 (90)	0.41

CFR, coronary flow reserve; TIMI, thrombolysis in myocardial infarction.

0.04; CV: 11.1%. The intraobserver variability were as follows: baseline coronary flow: mean difference: 0.001; 95% LOA: −0.028 to 0.03; CV: 3.6% and CFR: mean difference: −0.002; 95% LOA: −0.03 to 0.02; CV: 10.2%.

Angiographic and angioplasty data

Angiographic data in patient groups are seen in *Table 3*. In 49 patients, PCI was performed in the LAD; 45 patients achieved TIMI 3 flow in the LAD and 4 TIMI 0–2 flow. Drug-eluting stents were implanted in 109 patients and 45 patients received eptifibatid/abciximab infusion during and after the PCI procedure.

Discussion

The present study demonstrates that, early after an AMI, the microcirculation, in patients with successful revascularization, remains compromised in a large proportion of patients. Although resting LV function appears unaffected, patients with intact microcirculation are more likely to have viable myocardium suggestive of a better potential for functional recovery after AMI.

In the present study, CFR was assessed in the early post-AMI phase, which is opposed to most other studies where CFR was assessed in stable patients with known or suspected coronary artery disease. We found that CFR frequently was depressed. Apparently, this had little effect on resting LV size, regional, global, and longitudinal function. As many patients presented with minor LV damage and preserved global LV function, the study may lack power to detect subtle differences in resting function. This observation is in agreement with studies of stable patients with minor or normal LV function.[12–14] Importantly, these studies suggested a prognostic importance of CFR despite no apparent effect on LV function.

LDDE is well suited for the assessment of viability and assessment of contractile reserve.[15,16] As outlined in the expert consensus statement from the Association of Echocardiography,[17] the combination of LDDE and CFR assessment could be beneficial. Using this technique, we were able for the first time to detect several consequences of reduced CFR early after AMI. Although LV end-systolic volume at rest were similar in patients with a reduced CFR, we observed a significant difference during LDDE where end-systolic volume increased in patients with decreased CFR this was associated with a lack of improvement in WMSI. As opposed to this WMSI improved in patients with intact microcirculation.

Echocardiographic determination of myocardial motion by tissue Doppler is a reliable method for assessing the performance of longitudinal oriented LV fibres. These fibres are mainly distributed within the subendocardium,[18,19] rendering them vulnerable for ischaemic microvascular damage. This may explain our observation that patients with decreased CFR did not improve LV longitudinal function during LDDE. It could be speculated that this could increase the risk for LV dysfunction and adverse LV remodelling.[20,21]

In patients with resting wall motion abnormalities, we found CFR to be closely associated with myocardial viability. The data indicate that patients with microvascular dysfunction had a very low likelihood of having viable myocardium A previous study have suggested that the presence of myocardial viability is related to a more favourable outcome compared with those without viability.[22] This could provide an important link between CFR and risk stratification in patients suffering from AMI. Probably, the methods should be viewed as complementary rather than alternative diagnostic tools. An important finding in the present study is that the current management of AMI does not appear to restore microvascular integrity in a large proportion of patients.

The subgroup of patients with decreased CFR included patients with resting wall motion abnormalities as well as patients with preserved wall motion. We were not able to identify any variable that could explain the difference in wall motion in these patients. The difference in CFR may be explained by subendocardial decreased perfusion of limited extent to decrease regional CFR but not severe enough and/or transmurally extended to give rise to dysfunctional LV function, at least not enough to be characterized with echocardiography.[23–25]

Study limitations

Our findings may reflect increased microvascular dysfunction with increased macrovascular disease. As mentioned, our patients presented with minor LV damage and preserved global LV function which may be of great importance interpreting the data. Especially in relation to the viability testing in patients a near normal LV function. Both groups (normal and abnormal CFR) have a small dysfunction which may affect the results. Furthermore, beta-blocking agents were not withheld for ethical reasons and we cannot exclude that dobutamine sensitivity might have been affected. Furthermore, the relatively low median CFR observed may be a result of generalized myocardial microvascular impairment in post-AMI

patients. We only performed CFR assessment in the LAD which may lead to cautiousness interpreting the data concluding the general microvascular function, even though this did not seem to have any influence (*Table 3*). The reason for this approach was to illustrate the usefulness of CFR in conjunction with LDDE in a consecutive AMI population. It has been demonstrated with several techniques that microcirculatory dysfunction affects the left ventricle globally[26] therefore CFR assessment in the LAD is an acceptable option for evaluating global coronary microcirculation conditions.

Although assessment of CFR has been validated against invasive measures of CFR, the accuracy is influenced by image quality and angle dependence of Doppler velocities which may limit the correctness in the individual patient.

Clinical implications

In conclusion, the presence of viability by LDDE is associated with normal microvascular function and reserve. Our study strongly suggests that CFR measured non-invasively after AMI is an indicator of microvascular integrity and of myocardial viability. Decreased microcirculation was associated with an abnormal response of the ischaemic heart to LDDE. This study illustrates the relationship between CFR and LV systolic function. Further investigation of patients with decreased microcirculation is indicated.

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